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THE UNIVERSITY OF WISCONSIN
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DEPARTMENT OF MEDICAL GENETICS
SCHOOL OF MEDICINE
Please Reply To
GENETICS BUILDING

DEPARTMENT OF GENETICS
COLLEGE OF AGRICULTURE

October 10, 1958

Dr. F. M. Burnet
Hall Institute of Medical Research
Royal Melbourne Hospital
Parkville, N.2. Australia

Dear Mac:

Much thanks for yours of the 29th September. I suspect that a prolonged interchange on the finest points of hypotheses of antibody formation will eventually prove to be rather tedious and that the time is ripe for a certain amount of experimentation. However I could not refrain from 1) acknowledging the aptness of your first paragraph and 2) from making at least a feeble attempt to reply to some of your specific points of difference.

With regard to your item 1, I think that my revision covers the situation in the following way: the introduction of an antigen will result in the suppression of various cells which hypermutate into a homologous state and thereby remove them from the scene. However in a post-natal animal there will already be some cells that have matured past the stage of hypersensitivity and these cells will be stimulated to give the immune response. Lethally irradiated animals may still have a residue of mature reactive cells and one hopes that one may eventually be able to devise methods of coping with these as well, to induce tolerance in the adult.

For item 2, Medawar's experiment is of course fundamental to any hypothesis of tolerance. It shows that the tolerant state characterizes every relevant cell of the host animal and is not simply a matter of some humeral inhibitory factor. I would interpret this experiment as the introduction of a population on cells which includes some already preadapted to the antigenic stimulus of their new host and which have already matured so that they give the immune rather than the hypersensitive tolerant response. This would furnish one way of investigating the frequency of various cell types but I understand that the breakdown of tolerance still requires very substantial implants.

The rapid production of primary antibody might be explained in either of two ways: 1) Either these antibodies are really not primary, the animals having very likely experienced related antigenic stimuli from their own intestinal flora in the course of their lives or 2) the primary response here as in other situations results from the stimulation of cells preadapted to produce those species of antibody. I am not aware of any experiments that would put these antigens into a unique class as far as the induction of tolerance insofar as it may be necessary to use a persistent regime of innoculation to produce tolerance to any antigen which does not continually leak into the circulation from a living chimera.

Your remarks about universal variability lead me to think that you may have miscontrued the rate of hypermutability that needs to be proposed for the ~~hypo-~~ hypothesis. On the most conservative version this variation might take place only once at each cell division and have to do with the reconstruction of the DNA of the daughter chromosomes. Speaking for my own personal prejudices I find little to choose between a massive randomization that takes place at one characteristic epoch of development as against one which continues in a given stem line. Experiments on the totipotency of single clones may or may not furnish evidence against either of our statements of a genetic hypothesis. If that is the case we may still be able to resort to an elective hypothesis based on hypermutability of the very numerous microsomes. I hesitate to resort to this on the same grounds as your own objection qua Pauling but at least it would have the advantage of furnishing a more plausible pathway for the effect of foreign substances on the specific protein-synthesizing mechanisms of the cell.

You need have no fear for your progenitive reputation. I myself have not have so much fun and intellectual excitement for a long time and I am very much indebted to you for it.

I am of course pursuing my end of the game as far as getting Gus with us and am quite sure that one way or another something very useful will be managed.

You will notice another imprint of my Australian experience in the experiments we are doing now with periodate. It is quite definite that the specif c male reactivity of E. coli can be destroyed by this means although the target substance so far seems to be unaltered by RDE.

Yours as ever,

Joshua Lederberg

JL/jp

P.S. Our plans for moving are becoming more definite and it is now fixed that we will move into Stanford about February 1, 1959. These will be temporary quarters however and we will be away from the scene for an interval during the spring visiting Cavalli at Pavia. We should be ready to occupy our definitive quarters in the new medical center sometime in July. I suggest that it would be worth giving us a month or two to get the place in order before Gus comes but on this basis we actually could accommodate him as early as July 1 or July 15.

Is it too much to hope for that you may be traveling through San Francisco again sometime in the next year or two? If so I do nope you will not neglect to give us an opportunity to play host to you at that time. Perhaps this is not the best occasion to raise the spectre of more distractions.